REMARKS

This Amendment and Response is timely filed in response to the Office Action of February 16, 2001 because the Applicants are filing concurrently herewith a Petition for a Three-Month Extension of Time.

In the February 16, 2001 Office Action, the Examiner rejected pending claims 1-10, 67 and 83-86. Claims 1-10, 67 and 83-86 have been cancelled without prejudice to reassert the subject matter therein in a subsequent application. Claims 87-136 have been added with this amendment. These new claims are supported by the specification and add no new matter. Specifically, support for new claims 87-89 may be found at: page 14, lines 10-32; page 24, lines 8-19 and page 63, line 1 - page 82, line 8. Support for new claims 90-111 may be found at: page 8, line 27 - page 9, line 21; page 29, line 1 - page 34, line 28; page 82, line 10—page 85, line 25. Support for claims 112-136 may be found throughout the specification, e.g., at page 11, lines 2-23.

35 U.S.C. §112, ¶1 rejection

The Examiner rejected claims 1-10, 67 and 83-86 under sec. 112, ¶1 because, in the Examiner's view, the phrase "a member of the tumor necrosis factor family" and the word "gene" are not enabled by the specification.

The rejected claims have been cancelled and new claims 87-136 have been added which do not include either the objectionable phrase or word, thereby rendering the rejection moot. The Examiner is requested to reconsider and withdraw the rejection.

The Examiner also rejected claims 1-10, 67 and 83-86 under sec. 112, ¶1 because, in the Examiner's view, the phrase "partially derived accessory molecule ligand" is not enabled by the specification.

As noted above, claims 1 – 10, 67 and 83 – 86 have been cancelled, which renders the rejection moot. The Examiner is requested to withdraw the rejection.

35 U.S.C. §112, ¶2 rejection

The Examiner has also rejected claims 1-10, 67 and 83-86 under 35 U.S.C. §112, ¶2 because, in the Examiner's view, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. In particular, the Examiner is of the opinion that the phrase "altering the immunoreactivity" is vague and indefinite. The claims have been cancelled and new claims entered that more clearly point out that which Applicants consider the invention. The new claims do not contain the phrase "altering the immunoreactivity." The Examiner is requested to withdraw the rejection.

The Examiner rejected the claims 1-10, 67 and 83-86 for use of the phrase "increased stability" because the specification does not provide a standard for ascertaining the requisite degree. New claims 90, 124 and 136 specify that the stability of the claimed ligands are increased relative to the stability of a human CD40 ligand, whether transfected or native. Thus, the rejection is rendered moot and the Examiner is requested to withdraw it.

Applicants thank the Examiner for pointing out that the term TNFα was recited twice in claim 85; such is not the case in the new claims. The Examiner is requested to withdraw the rejection.

35 U.S.C. §102(b) rejection

The Examiner rejected claims 1-8, 10 and 83 under §102(b) as being anticipated by Yellin et al. because, in the Examiner's view, "this reference relies upon the T-BAM/CD40L expressing or transfected D1.1 cell line." The Examiner asserts that "the claimed methods of making CD40L transfected cells are met by the prior art" because "by making CD40L transfected cells, the ordinary artisan has altered the immunoreactivity of said cells by transfecting them with the costimulatory molecule CD40L."

Applicants respectfully traverse. The present claims have been cancelled and replaced with claims that more clearly point out that which Applicants consider their invention. The new claims recite methods that are not disclosed by Yellin. The first claimed method is transfecting human CD40+ cells – i.e., cells expressing a CD40 ligand receptor – with a nucleic acid sequence encoding non-human or chimeric CD40 ligand to induce expression of the encoded CD40 ligand. The second claimed method is transfecting human cells with a nucleic acid sequence encoding a chimeric CD40 ligand to increase the stability of the expressed ligand on the surface of the cells.

The Yellin reference does not describe the use of the same or similar nucleic acid sequences recited in the new claims. All of the Applicants' claims are directed to a non-human or chimeric CD40 ligand sequence. Yellin discloses neither nucleic acid sequence.

For these reasons, the Examiner is requested to reconsider and to withdraw the rejection.

35 U.S.C. §102(e) rejection over Spriggs, et al.

The Examiner rejected claims 1-10, 67 and 83 under 35 USC §102(e) as being anticipated by Spriggs et al. which, in the Examiner's opinion, teaches "transfecting human cells...with CD40L and modifications thereof for treatment." Spriggs relates to a treatment method comprising administration of soluble CD40L. The specification discloses a method using gene therapy to correct syndromes in which the CD40L gene does not encode biologically active CD40L. That is, cells deficient in CD40L are transfected with the CD40L gene so that they express biologically active CD40L capable of binding to CD40. (See col. 6, line 35 - line 42, et seq.)

The Applicants respectfully traverse this rejection. New claims 87-89, 91-123 and 125-135 expressly state that a key element of the invention is that the cells being transfected with CD40L are CD40+ cells. This element is not disclosed by Spriggs.

New claims 90-122, 124-134 and 136 expressly state that another element of the invention is increasing the cellular surface stability of a ligand capable of reacting with a CD40 ligand receptor, relative to that of a human CD40 ligand, via transfection of a cell with a nucleic acid sequence encoding a chimeric CD40 ligand. Spriggs does not teach transfecting cells with a nucleic acid sequence encoding a chimeric CD40 ligand.

For these reasons, the Examiner is requested to reconsider and to withdraw the rejection.

35 U.S.C. § 102(e) rejection over Marakovsky

The Examiner rejected claims 1-10, 67 and 83 under §102(e) as being anticipated by Marakovsky et al. because, in the Examiner's opinion, Marakovsky teaches "transfecting

human dendritic cells with CD40L and modifications thereof to augment responses to desired antigens." Once again, however, the method of altering immunoreactivity differs between the Marakovsky reference and the claims of the present invention. In Marakovsky, dendritic cells are stimulated to generate an immune response by transfecting them with a gene for an antigen against which an immune response is desired and exposing the transfected cells to a CD40 binding protein, such as soluble CD40 ligand.

The Applicants traverse this rejection because there are several differences between Marakovsky and the claims of the present invention. First, Marakovsky does not disclose any use of a nucleic acid sequence encoding a non-human or chimeric CD40 ligand, as are required by the new claims. Secondly, Marakovsky does not recite transfecting a human CD40+ cell, or transfecting a human cell to increase the stability of a ligand capable of binding to a CD40 ligand receptor on the surface of the cell.

For these reasons, the Examiner is requested to reconsider and to withdraw the rejection.

35 U.S.C. §103(a)

Claims 1-10, 67 and 83 are further rejected under 35 U.S.C. §103(a) as being unpatentable over Freeman et al, in view of Yellin et al. and Alderson et al. and/or the Spriggs and/or Marakovsky references. Applicants respectfully traverse this rejection because the combination of these references does not achieve the claimed invention and proper motivation does not exist to combine these references.

First, the combination of these references does not achieve the claimed invention. The Freeman et al. reference relates to transfection of tumor cells with genes encoding an

entirely different class of co-stimulatory molecules and corresponding receptors–i.e., the B7 molecule expressed on B cells and other antigen-presenting cells, and the CD28 and CTLA-4 receptors. The new claims of the present invention are directed to transfection with genes encoding specific TNF family members — i.e., human and/or murine CD40 ligand, TNF-alpha, TNF beta, Fas ligand, CD70, CD30 ligand, 4-1 BBL, Nerve growth factor beta, and TNF-related apoptosis inducing ligand (TRAIL). Although the Freeman reference mentions using variants of B7-2 and/or B7-3, including "a chimeric protein of the co-stimulatory molecule and another protein," there is no description, teaching or suggestion of using a chimeric gene to increase the stability of the resulting protein on the surface of the expressing cell.

Nor is this element disclosed by the Alderson reference, which describes altering the immunoreactivity of human monocytes–by co-culturing these monocytes with specific cytokines to enhance expression of CD40, or co-culturing these monocytes with CD40L to stimulate cytokine production. Neither method of immunostimulation is related to that recited by the claims of the present invention–i.e., transfection of a human CD40+ cell with a non-human or chimeric CD40 ligand sequence to induce expression of the encoded CD40 ligand, or transfection of a human cell with a chimeric CD40 ligand sequence to increase the cellular surface stability of the encoded ligand.

Finally, as described above, neither the Yellin, Spriggs or Marakovsky reference describe, teach or suggest the invention as recited by the new claims. In fact, the Yellin and Marakovsky references employ methods of altering immunoreactivity that do not even involve transfection of the immunostimulated cell. While the Spriggs reference addresses

transfection of T cells to induce expression of CD40L, it does not describe, teach or suggest a method of inducing expression of CD40L in CD40+ cells, or increasing the stability of a ligand capable of binding to a CD40 ligand receptor.

Further, Applicants respectfully submit that proper motivation or suggestion does not exist to combine these references in the manner suggested. As described above, three of the references do not even describe, teach or suggest transfection of a cell. Each of these three references is directed to a distinct objective, and there is no motivation to combine them: Yellin describes co-culturing B cells with CD4+ T cells to induce B cell expression of CD80 and CD23; Marakovsky describes inducing dendritic cells to present more antigen by exposing them to a CD40 binding protein; and Alderson describes inducing monocytes to express CD40 by co-culturing them with certain cytokines. Further, the Freeman reference addresses and solves its own problem: inducing T cells to express B7-2 and/or B7-3 via transfection techniques and, therefore, does not suggest a motivation to be combined with the teachings of Yellin, Marakovsky and/or Alderson. Likewise, the Spriggs reference involves its own distinct problem - inducing cells deficient in CD40L to express biologically active CD40L utilizing gene therapy techniques.

CONCLUSION

On the basis of the above, reconsideration and allowance of the application is believed to be warranted and such action is respectfully requested. If the Examiner has any questions or comments regarding this amendment, the Examiner is respectfully urged to contact the undersigned at the number listed below.

Respectfully submitted,

LYON & LYON LLP

Date: August 16, 2001

By: _____
G. Peter Albert, Jr.
Reg. No. 37,268

633 West Fifth Street, 47th Floor
Los Angeles, CA 90071-2066
Tel: (858) 552-8400